REMARKS

Entry of the foregoingAmendment, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are respectfully requested.

Entry of this Amendment and Reply is proper under 37 C.F.R. § 1.116, because the Amendment and Reply complies with matters of form raised in the outstanding Office Action and places the claims in better form for an appeal, should an appeal be necessary. The amendments to the claims are necessary and were not earlier presented because they are made in response to arguments raised in the final Office Action mailed December 15, 2004.

As correctly indicated in the Office Action Summary, claims 19-38 are pending in the application and are under consideration. Claims 19-38 stand rejected.

Claim 35 has herein been canceled without prejudice or disclaimer to the subject matter disclosed therein.

Claim 19 has been amended to delete certain recitations added in previous amendments and to incorporate language from claim 35. Thus, support for the amendment to claim 19 can be found at least in claims 19 and 35 as previously presented.

Claim 23 is amended to present the chemical formula therein with appropriate subscripts.

Claim 38 has been amended to correct a typographical error and to recite the full chemical name tributylphosphate in place of the abbreviation TNBP. Support for the expansion of the abbreviation may be found in the specification at least at page 24, line 31.

No new matter has been introduced by way of the present amendments to the claims. Applicants reserve the right to file a continuation or divisional application on any of the canceled or deleted subject matter.

I. Matters of form

Applicants acknowledge that the Examiner has withdrawn the former objection to claim 35. However, claim 38 has been newly objected to for a typographical error and for reciting the abbreviation TNBP. Claim 38 has been amended to insert a space between "diafiltration" and "before" and to recite tributylphosphate in place of TNBP. TNBP is a well known abbreviation for tributylphosphate, also called tri(*n*-butyl)phosphate. The chemical name tributylphosphate is given in the specification, for example, at page 24, line 31. Withdrawal of the objection is respectfully requested. None of these amendments are intended to limit the scope of claim 38 or any element recited therein.

II. Claim rejection under 35 U.S.C. § 103(a)

The previous rejection of claims 19-38 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Shabram et al., WO 96/27677 A2 ("Shabram"), in view of Berg, WO 98/33572 A1 ("Berg"), and Bondoc et al., *J. Indust. Micro. & Biotech.*, 20:317-322, 1998 ("Bondoc"), has been withdrawn. However, claims 19-38 now stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Shabram in view of Berg, Bondoc, and Blanche et al. WO98/00524 (represented in English by U.S. Patent No. 6,458,958, "Blanche"). The rejection set forth in the Office Action mailed December 15, 2004 is as stated in previous Office Actions with respect to Shabram, Berg, and Bondoc, only the citation of Blanche is new. This rejection is respectfully traversed.

Blanche was introduced, because Blanche allegedly teaches a bead size for gel filtration at column 8, lines 58-65. However, it is respectfully pointed out that in this paragraph, Blanche is actually describing beads for use in anion-exchange chromatography. By contrast, claim 19 formerly recited using beads having a diameter of 5 to 105 μm for gel

filtration chromatography. Nevertheless, claim 19 has been amended in order to expedite prosecution and to reduce the number of issues on appeal, should an appeal be necessary, by deleting certain recitations, including this recitation, that were previously added by amendment. Accordingly, the citation of Blanche for the purpose it was introduced is moot.

Below, Applicants respond to the arguments by the Office in the Office Action with reference to law and facts that prove that the rejection has been improperly maintained.

a. The Office has improperly applied the rejection according to the law.

The prior art fails to establish a proper prima facie case of obviousness. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

It is impermissible to first ascertain factually what applicants did and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct applicant's invention from such prior art. *Interconnect Planning Corp. v. Feil*, 150 U.S.P.Q. 54, 57 (C.C.P.A 1966); *In re Shuman*, 774 F.2d 1132, 1142-3, 227 U.S.P.Q. 543, 550 (Fed. Cir. 1985). In asserting this rejection, the Office has taken a primary reference (Shabram) that unequivocally teaches a very distinct method, and using impermissible hindsight, selectively picked secondary references that are purported to teach one individual modification or another in an attempt to reconstruct the presently claimed methods. However, further contemporaneous work published by the patentees of Shabram and the secondary references themselves show that there would have

been no motivation, and no reasonable expectation of success, to combine the secondary references as proposed by the Office.

The combination of Shabram with Bondoc, Berg and Blanche fails to support a prima facie case of obviousness. It follows from the foregoing statement of the law that it is not sufficient that individual modifications of the primary reference may be suggested in individual references, but all the necessary modifications must be suggested in combination as the claims must be considered as a whole. To bridge the distinctions between Shabram and the presently claimed methods requires not only that the prior art teach every element of the claimed invention separately, but the prior art must also provide some suggestion, motivation and evidence of a reasonable expectation of success for making all the necessary modifications of Shabram in combination. The proposed combination does not meet the requirements for a prima facie case of obviousness.

b. Obvious to try is not the proper standard.

Shabram describes a method for purifying adenoviral particles comprising two chromatographic steps. Both chromatographic steps of Shabram's method are distinct from the steps of the presently claimed methods. Shabram's method consists of a conventional gravity column DEAE anion exchange chromatography step, followed by an affinity chromatography step using a conventional column comprising immobilized zinc. Shabram does not teach the use of fluidized bed chromatography in their methods or the use of a gel filtration step and certainly not the presently claimed combination of a fluidized bed chromatography step with a gel filtration step. In 26 claims, Shabram recites every variation on their methods which is favorably described as an aspect of their invention, but, Shabram does not recite any combination of step that uses either of these. The disclosure of Shabram also fails to provide adequate motivation.

Claim 19 explicitly recites that a step of the present methods comprises fluidized bed chromatography. Shabram does not teach one to use fluidized bed chromatography in a method of purifying adenovirus. Rather, only one sentence in the whole of Shabram, at page 9, lines 13-15, even refers to fluidized bed chromatography, and then only as part of a generic listing of chromatographic methods. This one sentence lists nearly every technique known in the art to perform chromatography, *i.e.* conventional packed bed (gravity), high pressure liquid chromatography using radial or axial flow, and batch and fluidized bed as can be found in any number of basic books on chromatographic methods. Shabram's generic recitation of all existing chromatographic methods cannot be construed as more than an acknowledgement that the particular methods that Shabram is teaching exist within a universe of possible methods that they neither teach nor recommend.

At page 3 of the Office Action mailed on December 15, 2004, the Examiner has asserted that the foregoing argument fails to prove that one skilled in the art would not have considered fluidized bed chromatograph an alternative method. However, that is not the proper test under the law. After reading Shabram, it would be no more obvious to try fluidized bed chromatography as any other technique besides the conventional methods Shabram actually employs. The Federal Circuit has consistently held that **"obvious to try" is not to be equated with obviousness** under 35 U.S.C. § 103. *See, e.g., Gillette Co. v. S.C. Johnson & Son Inc.,* 16 U.S.P.Q.2d 1923, 1928, 919 F.2d 720 (Fed. Cir. 1990) (citing *In re O'Farrell,* 853 F.2d 894, 903-04, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1380, 231 U.S.P.Q. 81, 91 (Fed. Cir. 1986); and *Jones v. Hardy,* 727 F.2d 1524, 1530, 220 U.S.P.Q. 1021, 1026 (Fed. Cir. 1984)) (emphasis added).

An analysis of obviousness of a claimed combination must include consideration of the results achieved by that combination. *Gillette*, 16 U.S.P.Q.2d at 1928 (emphasis added). **Critical to the analysis is an understanding of the particular results achieved by the new combination.** *Id.* (citing *Interconnect Planning Corp.*, 774 F.2d at 1143, 227 U.S.P.Q. at 551).

As an example, Shabram fails to appreciate and does not even suggest the surprisingly improved results that Applicants have achieved by the presently claimed methods and disclosed in the subject specification. Applicants have demonstrated a yield of infectious particles in a fluidized bed chromatography step of about 82% from lysate. *See* Specification at 26. In the article by Hughye et al. (*Human Gene Therapy*, 6:1403; 1995, previously submitted as an Exhibit to the Amendment and Reply filed March 30, 2004), Shabram and coworkers report a stepwise yield of only 49% infective particles. *See* Hughye et al. at 1412. (Note that the infective particle yield at page 1412 and not the total particle yield reported at page 1411 of Hughye et al. is comparable to the results in the present specification, which are reported in IU.) Shabram fails to even hint at an appreciation that using fluidized bed chromatography as in the presently claimed methods may provide such an advantage. This deficiency, among others, is not cured by combination with any or all of the secondary references.

Shabram's own published research teaches against the presently claimed combination.

Further, the clear quantitative results of the Shabram lab's comparative studies of various techniques teach away from modifying Shabram's method to arrive at the presently claimed combination. Shabram and coworkers investigated several types of chromatographic techniques for the purification of recombinant adenovirus particles. Huyghe et al., *supra*,

reports a comparative analysis of various techniques as part of the Shabram laboratory's efforts to develop the method for purification of adenovirus disclosed in the Shabram patent application. In particular, anion exchange, gel filtration (*i.e.,* size exclusion), hydrophobic interaction and metal chelating resins were tested. Shabram and coworkers teaching considered as a whole, would discourage one skilled in the art from combining the steps of the presently claimed method.

Of particular note, Dr. Shabram and his co-workers reported that the recovery of adenovirus from a gel filtration column was very low, only 15-20% of the virus injected being recovered. *See* Hughye et al. at page 1408 under "size exclusion chromatography." One skilled in the art would not be motivated to combine such a poor yielding step with any other step.

d. Bondoc does not cure Shabram's own teaching away.

At page 4 of the Office Action mailed December 15, 2004, the Examiner has contended that the results of Huyghe et al. are not relevant to the claimed method because the results of the single method would not expected to have the same result as the combination. The Examiner contends that the requisite motivation to use a gel filtration step comes from Bondoc.

Bondoc does refer to Shabram and coworkers Hughye et al. for his method and did use size exclusion chromatography step in place of Hughye's recommended zinc chelating chromatography step despite Hughye's miserable results. However, purification of adenovirus is merely incidental to Bondoc's goals, because Bondoc et al. relates specifically to the determination of adenovirus size by disc centrifugation. As a result, it is not surprising that Bondoc provides only the barest description of purification methods. Bondoc fails to identify the matrix used for its gel exclusion step, thus Bondoc does not teach all the elements

the gel filtration step recited in claim 19. Further, Bondoc fails to describe how well or poorly the gel filtration step works.

In view of Bondoc's limited relationship to adenovirus purification and considered in the context of Hughye, one skilled in the art would not look to Bondoc to learn how to modify Shabram. Further, the clear teaching of Hughye, which argues strongly against what Bondoc has attempted, would nullify any interest in using a gel filtration step in a method based on Shabram that Bondoc might purportedly suggest. Moreover, Bondoc certainly does not suggest the combination of further modifications to Shabram that would be necessary to arrive at the presently claimed combination.

e. Blanche does not cure the deficiencies of the combination of Bondoc and Shabram.

Blanche teaches a method of producing adenovirus using conventional methods of purification which is distinguished by and limited to the case where particles are recovered from cell culture supernatant without a cell lysis step, and further where the supernatant is concentrated using an ultrafiltration step prior to chromatography.

Blanche does not teach or suggest a fluidized bed chromatography step, or even mention fluidized bed chromatography. Blanche provides an example of ion exchange chromatography using supernatant of an adenovirus infected cell culture that has been processed by an ultrafiltration step. Blanche achieves only a 65% yield in plaque forming units using this process. This appears to be better than Shabram, but remains well below the surprising results demonstrated by the presently claimed methods.

Interestingly, Blanche takes note of Shabram and coworker's "study of the use of gel permeation chromatography, demonstrating a very poor resolution and very poor low yields (15%-20%)." *See* Blanche at col. 3, lines 50-53. In acknowledgement of this, Blanche's

suggested use of gel permeation is limited to very specific circumstances. Blanche provides an example method using only 200 µl of supernatant processed by an ultrafiltration step prior to conventional gel permeation, optionally coupled with conventional ion exchange chromatography. Blanche further distinctly requires a two step gel permeation protocol using two different gel permeation columns in series. Even so, Blanche reports that the collected peak contains 25% contamination. *See* Blanche Example 6.

From the foregoing, it is clear that the combination of all the cited references that actually address adenoviral preparation (Shabram, Bondoc, and Blanche) does not teach or suggest the presently claimed combination. One of skill in the art has received no motivation to use a fluidized bed chromatography step beyond that it may be as obvious to try as any chromatographic technique. Moreover, considering all of Shabram, Bondoc and Blanche in the context of Hughye et al., the teachings in the art regarding gel filtration is very equivocal, with Shabram weighing strongly against its usefulness, Bondoc being neutral where purification is tangential to the goal, and Blanche teaching its application in very limited circumstances but resulting in retention of 25% contamination.

f. Berg, which does not address adenoviral preparation, does not cure the deficiencies of Shabram, Bondoc, and Blanche.

The Office has contended that Berg's teaching of fluidized bed chromatographic techniques for separating a "substance" from a liquid sample using particles of adsorbent equipped with flexible extenders coated with a ligand having affinity to the substance provides the motivation and teaching to modify Shabram.

However, Berg's general purpose teaching makes it no more obvious to try fluidized bed chromatography in a method of preparing adenovirus than any other chromatography technique, all of which have their proponents for general purposes. Berg does not teach or

suggest whatsoever that a fluidized-bed process could be effective for virus purification, and even less for adenovirus purification. Berg does not even hint at the surprising results that Applicants have obtained and disclosed in the present application.

Applicants have pointed out that adenoviral particles are far more complex than the macromolecules considered as suitable for fluidized bed separation by Berg. Moreover, Berg explicitly teaches that the fluidized-bed chromatography process *"is normally* ***limited*** to *the adsorption/separation of compounds that have* ***a molecular weight below 1,000,000 Daltons."*** (*See* Berg at page 12, lines 13-16 (emphasis added). Adenoviral particles have a molecular weight of approximately $1.5x10^8$ Da, *i.e.,* more than two orders of magnitude or about 150 fold above the normal limitation of the method as taught by Berg

The Office has asserted that this teaching does not exclude application to adenoviruses. To support a prima facie case of obviousness, a reference or references must provide motivation to make a combination. *See, e.g,.* M.P.E.P. § 2143. It therefore follows that merely failing to exclude the possibility is not the proper test under the law.

Berg fails to provide any specific teaching or suggestion that would motivate one of skill in the art to modify Shabram as proposed in the rejection. At the very least Berg teaches that it would have been considered unusual (and therefore not obvious) to utilize fluidized-bed chromatography for a compound substantially greater than $1x10^6$ Da. Given the more than two orders of magnitude above the normal molecular weight limit given by Berg of the molecular weight of an adenoviral particle, according to Berg, it would be highly unusual and thus there would have been no reasonable expectation of success in using adsorbent particles of Berg to achieve a good purification profile and retain most of the virus infectivity, let alone the surprising results that can be achieved using the presently claimed method.

The teaching of Berg does not support a prima facie case of obviousness as applied to the present claims. Berg does not teach or suggest combining a fluidized bed chromatography step with any other step, and certainly does not suggest the combination of modifications to Shabram that would be required to arrive at the present invention. The teaching of Berg has no particular relation to the teaching regarding adenoviral purification of Shabram, Bondoc, and Blanche. The Office has shown no apparent motivation for one of skill in the art of viral preparation to look to Berg for teaching among all the proponents of various chromatographic techniques.

g. The combination of references as a whole do not render the claims unpatentable.

Taking all the art together, the prior art fails to support a prima facie case of obviousness. Accordingly, Applicants respectfully request that the rejection of claims 19-38 under 35 U.S.C. § 103(a) be withdrawn.

III. Conclusion

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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